REMARKS

This response is identical in substance to the response filed September 17, 2006. The claim identifier for claim 38 has been amended to indicate that the claim is currently amended.

Claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 were pending in the application. Claims 1, 5, 38, 41, 112, and 113 have been amended an new claims 96-99 have been added. Accordingly, after the amendments presented herein have been entered, claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 will be pending.

Support for the amendments can be found throughout the specification and claims as filed.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of claim 112 under 103(a)

The Examiner has rejected claim 112 under 35 USC 103(a) as being unpatentable over 5,859,312 ("Littman et al.") in view of Monbarts et al. The Examiner indicates that claim 112 was never amended to include the limitation that the human T cell receptor loci are unrearranged and that the transgenic non-human mammal comprises human alpha and beta chains as was claim 1.

Applicants have amended claim 112 in line with claim 1. Therefore, Applicants believe that this rejection is rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 103(a)

The Examiner has rejected claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 USC 103(a) as being unpatentable over 5,859,312 ("Littman et al.") in view of Monbarts et al., McMurry et al., Rowen et al. and Rack et al.

Applicants traverse this rejection for the following reasons.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As described in detail below, and in addition to other deficiencies, none of the cited references teach transgenic animals that carrying human TCR loci that ***capable of undergoing productive rearrangement.***

Littman et al. has a very broad general disclosure that does not enable one of skill in the art to make and/or use transgenic animals carrying TCR loci that are capable of undergoing productive rearrangement. Additionally, the teachings of the secondary references do not make up for this deficiency in Littman et al.

It was well-understood at the time of the invention that B cells, αβ T cells and γδ T cells are of distinct cell lineages displaying rearrangements of individual antigen receptor loci. Furthermore it was known that developing αβ and γδ T cells tightly regulate the rearrangement of the respective TCR loci and that this rearrangement occurs in an lineage and developmental stage dependent manner in relationship to different TCR loci as well as the specific events within each loci. For example, McMurry et al. state that in developing T cells, the β, γ and δ loci rearrange prior to the α loci and that TCR β loci D to J rearrangement precedes V to DJ rearrangement (see page 4453 second column). In fact the initiation of TCR α loci rearrangement is dependent on previous productive rearrangement of the TCR β loci and expression of the TCR β chain in the pre-T cell receptor. In addition there are a number of other notable differences exist between the developmental regulation of assembly of αβ and γδ TCR variable region genes (see for example Godfrey et al. 1993. Immunology Today 14:547-553 and Lauzurica & Krangel. 1994. J. Exp. Med. 179:1913-1921; copies of which are provided herewith and Appendices A and B). Thus the regulatory events and signal elements controlling human TCR α and β loci rearrangement are very different from those directing the TCR delta minilocus rearrangement of McMurry et al. in terms of their cell type dependence, developmental timing and other requirements.

Further, the examiner maintains that McMurry et al. supplements Littman by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. The Examiner further states that McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human multiple V, D, J and C gene segments and that transgenic mice are capable

of functionally rearranging the human TCR delta minigene locus. Again, this is not correct. While McMurry et al. showed that rearrangement of the TCR delta minigene locus, neither functionality nor productivity (i.e. in-frame gene sequence) of these rearrangements was demonstrated.

It was well-understood at the time of the invention that B cells, αβ T cells and γδ T cells are of distinct cell lineages displaying rearrangements of individual antigen receptor loci. Furthermore it was known that developing αβ and γδ T cells tightly regulate the rearrangement of the respective TCR loci and that this rearrangement occurs in an lineage and developmental stage dependent manner in relationship to different TCR loci as well as the specific events within each loci. For example, McMurry et al. state that in developing T cells, the β, γ and δ loci rearrange prior to the α loci and that TCR β loci D to J rearrangement precedes V to DJ rearrangement (see page 4453 second column). In fact the initiation of TCR α loci rearrangement is dependent on previous productive rearrangement of the TCR β loci and expression of the TCR β chain in the pre-T cell receptor. In addition there are a number of other notable differences exist between the developmental regulation of assembly of αβ and γδ TCR variable region genes (see for example Sleckman et al. 1998. J. Exp. Med.. 188: 1465; a copy of which is provided herewith). Thus the regulatory events and signal elements controlling human TCR α and β loci rearrangement are very different from those directing the TCR delta minilocus rearrangement of McMurry et al. in terms of their cell type dependence, developmental timing and other requirements.

Moreover, the transgenic mice of McMurry carry only a single transgenic TCR delta minilocus and do not carry the either human TCR beta or alpha loci. As such, rearrangement of the transgenic TCR minilocus of McMurry would be expected to be regulated in a different signals and in a different cell lineage pathway than the human TCR α and β loci of the invention. Furthermore, Littman does not disclose generation of transgenic mice containing unrearranged human TCR alpha and beta loci or generation of transgenic mice capable of productively rearranging human TCR loci. Given the known differences between the developmental regulation of antigen receptor loci rearrangement, one skilled in the art would not rely on the teachings of Littman supplemented by McMurry to generate a transgenic animal comprising unrearranged human T-cell receptor α and β loci capable of productively rearranging

the transgenic TCR loci and producing heterologous T-cell receptor, as required by the claims in the instant application.

Finally, the structure of the human TCR β and α loci are very different from the TCR delta minilocus described by McMurry. As taught by Rowen et al., the TCR beta locus is very complex and consists of multiple functional TCR beta gene segments (including multiple C domain sequences and inverted V domain sequences) and pseudogene segments as well as other trypsinogen genes interspersed within the TCR gene segments. Furthermore, Rack et al. describe the TCR alpha/delta locus as unusual insofar as the TCR delta genes are situated within the TCR alpha locus (page 1233 first column). These complexities would be expected to affect the ability of the TCR α and β loci to productively rearrange. These complexities are not present in the TCR delta minilocus of McMurry. In addition the TCR α loci also differs from the TCR delta minilocus in that the TCR α loci does not contain D elements. These difference in loci structure and complexity would dissuade one skilled in the art from relying on the teaching of McMurry et al. from predicting successful generation of a transgenic animal comprising unrearranged human T-cell receptor α and β loci capable of productively rearranging the transgenic TCR loci and producing heterologous T-cell receptor.

In addition, the teachings of Rowen et al. and/or Rack et al. do not make up for the deficiency in Littman et al. and McMurry. Neither Rowen et al. nor Rack et al. teach use of nucleic acids encoding unrearranged TCR β and α loci in a transgenic animal wherein said animal is capable of productive rearrangement of the TCR α and β loci.

Accordingly, based on the foregoing, one of skill in the art would not arrive at the claimed invention by relying on the teachings of Littman et al. McMurry et al., Mombaerts et al., McMurry et al., Rowen et al. and Rack et al. Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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